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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,821	10/16/2003	Eric Wickstrom	W11333/20008	2530

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/30/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83 and 85-87* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,17-25,35-40,46,47,53,57-68,74 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,16,26-34,41-45,48-52,54-56,69-73,75-83,85 and 86* is/are rejected.

7)☒ Claim(s) *69-73,75 and 85-87* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants' election of the invention of Group I, drawn to a diagnostic method that uses a compound comprising a diagnostic moiety conjugated to at least one PNA and at least one targeting moiety, wherein the PNA comprises a base sequence complementary to a target nucleic acid sequence, is acknowledged. Applicants' species election of K-RAS, peptide, chelant, DOTA, metal ion, Gd(III), dendrimer, and PMAM is also acknowledged. Election was made without traverse in the reply filed on 03/30/2006.

Claims 5, 6, 15, 17, 18-20, 21-25, 35-40, 46, 47, 53, 57-68, 74, and 87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim.

Claims 1-4, 7-12, 13, 14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75-83, 85, and 86 are pending.

Note: Change in Art Unit and SPE

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

Claim Objections

2. The numbering of claims is not proper because claim 84 is missing. Correct renumbering of the claims is required.

3. Claims 69-73, and 75 are objected to because they recite "a compound of claim 1". Appropriate correction to "the compound of claim 1", such that the claims encompass the scope of claim 1, is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

4. Claims 76-82 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: comparison to a control (i.e., there is no correlation between the presence of the compound inside the cells and the overexpression of the transcript in said cell).

Claims 76-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear, and the specification does not disclose, what characteristics are expected of a cell such that it is suspected of overexpressing the transcript.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4, 28-32, 34, 69, 71-73, 76, 80, 81, 83, 85, and 86 are rejected under 35 U.S.C. 102 (b) as being anticipated by Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), as evidenced by Basu et al. (Bioconjugate Chem, 1997, 8: 481-488).

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript. Lewis et al. teach that cells expressing high levels of *bcl-2* internalize significantly more conjugate as compared to cells expressing low *bcl-2* levels, i.e., the presence of the conjugate inside the cells indicates overexpression of the *bcl-2* transcript (p. 1178, column 2 bridging p. 1179). With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are

covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition. With respect to the linkers recited in claim 3, absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. Since Lewis et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

Claims 1, 2, 4, 7-10, 12-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 are rejected under 35 U.S.C. 102 (b) as being anticipated by Tomalia et al. (US Patent No. 5,714,166), as evidenced by Basu et al.

Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer such as PMAM (i.e., a branched oligomeric polychelant), M represents a carried material, T represents a targeting moiety that can be an antibody fragment such as Fab, Fab', and wherein M and T are associated with the dendrimer via the same or different linkers (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 52, lines 57-60). Tomalia et al. teach that M can be a PNA (column 47, lines 1-10) and that two or more dendrimers can be associated with each other

(covalently bridged or through other associations), i.e., the diagnostic moiety comprises a plurality of chelants (column 3, lines 22-40, column 13, lines 5-11, column 45, lines 1-9) and optionally can comprise additional agents that could be diagnostic metal ions, (column 1, lines 59-65, column 22, lines 15-35, column 88, Example 24, column 89, Table XI). Tomalia et al. teach that the compound can be used either *in vitro* or *in vivo* as a cancer therapeutic and diagnostic agents for noninvasive imaging and for transferring of genetic material, such as PNA into cells to block the production of specific proteins (column 28, lines 28-40, column 39, lines 25-30, column 54, lines 8-18, claim 32), i.e., Tomalia et al. teach a method of retaining a compound inside the cells for diagnostic or therapeutic purposes. For *in vivo* use, the compound can be administered into the portal vein, i.e., intravascular administration (column 54, lines 10-15). With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition. Since Tomalia et al. teach all the limitations recited in the claims, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 4, 7-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., as applied to claims 1, 2, 4, 7-10, 12-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 above, in view of Meade et al. (US Patent No. 6,713,046).

Although Tomalia et al. do not specifically teach a PMAM-PNA compound wherein the PMAM comprises gadolinium, they do teach that their dendrimer can be optionally associated with more that one agent (see above), and that they can be used for both therapeutic and diagnostic purposes; such compounds can be detected by MRI (column 28, lines 28-35, claim 32). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to include gadolinium into the PMAM-PNA conjugate of Tomalia et al. for noninvasive MRI imaging in a subject, with a reasonable expectation of success. The motivation to do so is provided by Meade et al. who teach that Gd(III) is the preferred contrast agent for MRI because it has a very high magnetic moment and a symmetric electronic ground state (column 2, lines 34-49). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful incorporation of Gd(III) into dendrimers for MRI imaging. Thus, the claimed invention was anticipated by the above cited art.

Tomalia et al. do not teach a biodegradation cleavage site. Meade et al. teach a biodegradation cleavage site (column 14, lines 20-30). It would have been obvious to one of skill in the art, at the time the invention was made, to include a biodegradation

cleavage site, as taught by Meade et al, with a reasonable expectation of success. The motivation to do so is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. One of skill in the art would have been expected to have a reasonable expectation of success because Meade et al. teach the successful use of such sites. Thus, the claimed invention was anticipated by the above cited art.

Claims 1-4, 28-32, 34, 69, 71-73, 76-81, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., as applied to claims 1-4, 28-32, 34, 69, 71-73, 76, 80, 81, 83, 85, and 86 above, in view of Tomalia et al.

Lewis et al. taken with Basu et al. do not teach dendrimers or a plurality of chelants, or K-RAS. Tomalia et al. teach that PNA can be conjugated to dendrimers or a plurality of denrimers, i.e., a plurality of chelants (column 3, lines 22-40, column 13, lines 5-11, column 41, lines 28-34, column 45, lines 1-9, column 47, lines 1-10) for delivery of diagnostic compounds, such as Gd(III) into cells. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al. by using Gd(III) chelated to one or multiple dendrimers, as taught by Tmalia et al., with a reasonable expectation of success. The motivation to use dendrimers is provided by Tomalia et al., who teach dendrimers as being very efficient in delivering agents to cells. The motivation to use a plurality of chelants is aldo provided by Tomalia et al., who teach that such compounds can be used to deliver

multiple agents to cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful maker and use of such compositions. Thus, the claimed invention was anticipated by the above cited art.

Claims 1-4, 28-34, 69, 71-73, 76-83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al. and Tomalia et al., as applied to 1-4, 28-32, 34, 69, 71-73, 76-81, 83, 85, and 86 above, in further view of Nakano et al. (Molecular Therapy, 2001, 3: 491-499).

Lewis et al. taken with Basu et al. and Tomalia et al. do not teach K-RAS. Nakano et al. teach gene transfer antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to use a dendrimer-PNA according to the combined teachings of Lewis et al. and Tomalia et al., wherein the PNA is directed against K-*ras* to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to overexpress K-*ras*, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the overexpression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is overexpressed in many cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful

use of such methods. Thus, the claimed invention was anticipated by the above cited art.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa

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